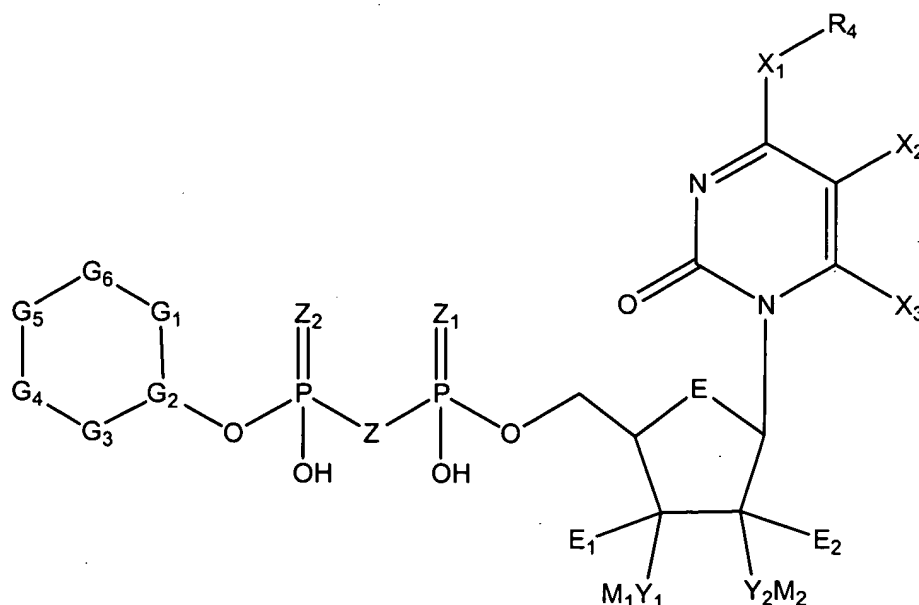


THE AMENDMENTS

- (Currently Amended) A method of reducing intraocular pressure comprising administering to a subject a pharmaceutical composition comprising an effective amount of a compound of Formula I, its ~~diastereomers~~ diastereomers, enantiomers, tautomers, or pharmaceutically acceptable salts thereof:



wherein:

$X_1 = O, NR, S, CF_2, CF_3$ or CN with the proviso that when $X_1 = CF_3$ or CN , then R_4 is absent; or X_1 represents a bond from the pyrimidine ring to R_4 or S ;

$X_2 = H, F, Cl, Br, I, CN, OR_8, SR_8, NR_9R_{13}, CF_3$, or alkyl, cycloalkyl, arylalkyl, aryl, arylalkenyl, arylalkynyl, $C(O)R_{16}$, $C(O)OR_{17}$, $C(O)NR_{16}R_{18}$ or heterocycle of 5 to 7 members;

$X_3 = H, CN, OR_{19}, SR_{19}, NR_{23}R_{28}, CF_3$, alkyl, cycloalkyl, $C(O)R_{32}$, $C(O)OR_{33}$, $C(O)NR_{34}R_{35}$, arylalkyl, aryl, arylalkenyl, arylalkynyl, or a heterocycle of 5 to 7 members;

$R = H, OR_1$, alkyl, cycloalkyl, arylalkyl, aryl, $C(O)R_2$, $C(O)OR_3$ or $C(O)NR_1R_2$;

$R_1, R_7, R_{10}, R_{22}, R_{24}, R_{27}, R_{31}, R_{33}$ and R_{35} are each independently H , alkyl, cycloalkyl, arylalkyl or aryl;

R_2 = H, alkyl, cycloalkyl, arylalkyl, aryl or heterocyclic ring of 5 to 7 members; or
 R_1 and R_2 taken together can form a heterocyclic ring of 5 to 7 members;
 $R_3, R_6, R_8, R_{12}, R_{15}, R_{17}, R_{21}, R_{26}$ and R_{30} are independently alkyl, cycloalkyl, arylalkyl or aryl;
 R_4 = H, alkyl, cycloalkyl, arylalkyl, aryl, heterocyclic ring of 5 to 7 members, $C(O)R_5$,
 $C(O)OR_6$ or $C(O)NR_5R_7$;
 $R_5, R_{11}, R_{14}, R_{16}, R_{18}, R_{20}, R_{25}, R_{29}, R_{32}$ and R_{34} are independently H, alkyl, cycloalkyl, arylalkyl,
aryl or heterocyclic ring of 5 to 7 members;
 R_9 = H, OR_{10} , alkyl, cycloalkyl, arylalkyl, aryl, $C(O)R_{11}$, $C(O)OR_{12}$ or $C(O)NR_{10}R_{11}$;
 R_{13} = H, alkyl, cycloalkyl, arylalkyl, aryl, $C(O)R_{14}$ or $C(O)OR_{15}$;
 R_{19} = alkyl, cycloalkyl, arylalkyl, or aryl, $C(O)R_{20}$, $C(O)OR_{21}$ or $C(O)NR_{20}R_{22}$;
 R_{23} = H, OR_{24} , alkyl, cycloalkyl, arylalkyl, aryl, $C(O)R_{25}$, $C(O)OR_{26}$ or $C(O)NR_{25}R_{27}$;
where R_{26} and R_{29} taken together can form a heterocyclic ring of 6 or 7 members;
or R_2 and R_4 , R_2 and R_5 , R_{10} and R_{11} , R_9 and R_{13} , R_{10} and R_{13} , R_9 and R_{14} , R_{11} and R_{14} , R_9 and
 R_{15} , R_{11} and R_{15} , R_{16} and R_{18} , R_{20} and R_{22} , R_{25} and R_{27} , R_{23} and R_{28} , R_{24} and R_{28} , R_{25} and R_{28} ,
 R_{25} and R_{29} , R_{29} and R_{31} or R_{34} and R_{35} are optionally taken together to form a heterocyclic ring
of 5 to 7 members;
 E = O or CH_2 ;
 E_1 and E_2 independently are H or F; or
 E_1 and E_2 , when taken together, form a carbon-carbon bond;
 Y_1 = O or F, with the proviso that when Y_1 = F, then M_1 is absent; or
 Y_1 represents a bond from the point of ring attachment to M_1 ;
 Y_2 = O or F, with the proviso that when Y_2 = F, then M_2 is absent; or
 Y_2 represents a bond from the point of ring attachment to M_2 ;
 M_1 and M_2 are independently H, alkyl, cycloalkyl, arylalkyl, aryl, $C(O)M_3$, $C(O)OM_4$, or
 $C(O)NM_3M_5$;
 M_3 = H, alkyl, cycloalkyl, arylalkyl, aryl or heterocyclic ring of 5 to 7 members;
 M_4 = alkyl, cycloalkyl, arylalkyl or aryl;
 M_5 = H, alkyl, cycloalkyl, arylalkyl, or aryl; or
 M_3 and M_5 taken together form a heterocyclic ring of 5 to 7 members;
when $Y_1 = Y_2 = O$, M_1 and M_2 optionally are bonds from the oxygen atoms of Y_1 and Y_2 ;

~~respectively, to a carbon atom of an acetal, ketal or orthoester group E₃;~~

~~wherein E₃ is Q(A₁)(A₂);~~

~~wherein Q is a carbon atom;~~

~~A₁ = H, CF₃, alkyl, cycloalkyl, arylalkyl or aryl;~~

~~A₂ = H, OA₃, CF₃, alkyl, cycloalkyl, arylalkyl, aryl or heterocycle of 5 to 7 members;~~

~~A₃ = alkyl, cycloalkyl, arylalkyl or aryl; or~~

~~where A₁ and A₂, when taken together, form a carbocyclic ring of 5 or 6 members, with or without unsaturation, and with or without substitution; or~~

~~M₁Q(A₁)(A₂)M₂ is taken together to form a carbonyl bonded to Y₁ and Y₂, such that a cyclic carbonate is formed;~~

~~Y₁M₁ and Y₂M₂ are independently OH, F, or H;~~

~~Z = O, NZ₃NH, CH₂, CHF, CF₂, CCl₂, or CHCl;~~

~~Z₁ and Z₂ are independently O or S;~~

~~Z₃ = H, alkyl, cycloalkyl, arylalkyl, aryl or a heterocyclic ring of 5 to 7 members;~~

~~G₁ = O, S, CH₂ or CH(OJ₁) or S;~~

~~G₂ = CH, C(CH₂OJ₃), CCH₃, CCF₃, or C(CO₂J₄);~~

~~G₃ = CH₂, CHF, CF₂, CH(OJ₅) or CH(NJ₆J₇) CH(OH) or CH(NHJ₇);~~

~~G₄ = CH₂, CHF, CF₂, CH(OJ₉), or CH(NJ₁₁J₁₃) CH(OH) or CH(NHJ₁₃);~~

~~G₅ = CH₂, CHF, CF₂, CH(OJ₁₅), or CH(NJ₁₆J₁₇) CH(OH) or CH(NHJ₁₇);~~

~~G₆ = CH₂, CH(CH₃), CH(CHF₂), CH(CF₃), CH(OJ₁₉), CH(CH₂OJ₁₉), CH(CH₂OH);~~

~~CH(CH₂(NJ₂₁J₂₂)), or CH(CO₂J₂₂), with the provision that when G₁ = O or S, then G₆ does not equal CH(OH); and~~

~~the number of hydrogen atoms bonded to the G₁-G₆ ring atoms is limited to a maximum of 8;~~

~~also with the provision that the number of nitrogen atoms bonded to the G₁-G₆ ring atoms in~~

~~Formula I is limited to a maximum of 2;~~

~~J₁ = H, alkyl, cycloalkyl, arylalkyl, aryl, or C(O)J₂;~~

~~J₂, J₆, J₈, J₁₀, J₁₁, J₁₄, J₁₆, J₁₈, J₂₀, J₂₂, and J₂₄ are independently H, alkyl, cycloalkyl, arylalkyl, aryl or heterocyclic ring of 5 to 7 members;~~

~~J₃ = alkyl, cycloalkyl, arylalkyl, aryl or C(O)J₂;~~

~~J₄ = alkyl, cycloalkyl, arylalkyl, aryl or heterocyclic ring of 5 to 7 members;~~

$J_5 = \text{H, alkyl, cycloalkyl, arylalkyl, aryl, or } \text{C}(\text{O})J_6$;

$J_7, J_{13}, \text{ and } J_{17} = \text{H, alkyl, cycloalkyl, arylalkyl, aryl or } \text{C}(\text{O})J_8$ are independently H, C(O)H, or C(O)alkyl;

$J_9 = \text{H, alkyl, cycloalkyl, arylalkyl, aryl, } \text{C}(\text{O})J_{10}, \text{CH}(\text{CH}_3)(\text{CO}_2J_{11}), \text{ or } \text{CH}(\text{CH}_3)(\text{C}(\text{O})\text{NJ}_{11}J_{12})$;

$J_{12} = \text{H, alkyl, cycloalkyl, arylalkyl, aryl, heterocyclic ring of 5 to 7 members, an amino acid radical of 2 to 12 carbon atoms with or without hetero atoms, or a peptide radical comprising 2 to 10 amino acid units}$;

$J_{13} = \text{H, alkyl, cycloalkyl, arylalkyl, aryl or } \text{C}(\text{O})J_{14}$;

$J_{15} = \text{H, alkyl, cycloalkyl, arylalkyl, aryl or } \text{C}(\text{O})J_{16}$;

$J_{17} = \text{H, alkyl, cycloalkyl, arylalkyl, aryl or } \text{C}(\text{O})J_{18}$;

$J_{19} = \text{H, alkyl, cycloalkyl, arylalkyl, aryl or } \text{C}(\text{O})J_{20}$;

$J_{21} = \text{H, alkyl, cycloalkyl, arylalkyl, aryl, } \text{C}(\text{O})J_{22} \text{ or heterocyclic ring of 5 to 7 members}$;

$J_{23} = \text{H, alkyl, cycloalkyl, arylalkyl, aryl or } \text{C}(\text{O})J_{24}$; or

J_6 and J_7, J_{11} and J_{12}, J_{11} and J_{13}, J_{16} and J_{17} or J_{21} and J_{23} are optionally taken together to form a heterocyclic ring of 5 to 7 members; or

where J_{22} and J_{24} , when taken together, form a heterocyclic ring of 5 to 7 members or a bicyclic imide comprising 4 to 12 carbons, with or without unsaturation and/or with or without substitution; or

when $G_1 = \text{CH}(\text{O}J_1)$ and $G_2 = \text{C}(\text{CH}_2\text{O}J_3)$, J_1 and J_3 optionally are bonds from the oxygen atoms of G_1 and G_2 , respectively, to a carbon atom of an acetal, ketal or orthoester group G_7 ; wherein $G_7 = \text{Q}_1(\text{T}_1)(\text{T}_2)$; or

when $G_2 = \text{C}(\text{CH}_2\text{O}J_3)$ and $G_3 = \text{CH}(\text{O}J_5)$, J_3 and J_5 optionally are bonds from the oxygen atoms of G_2 and G_3 , respectively, to a carbon atom of an acetal, ketal or orthoester group G_8 ; wherein $G_8 = \text{Q}_1(\text{T}_1)(\text{T}_2)$; or

when $G_3 = \text{CH}(\text{O}J_5)$ and $G_4 = \text{C}(\text{CHO}J_9)$, J_5 and J_9 optionally are bonds from the oxygen atoms of G_3 and G_4 , respectively, to a carbon atom of an acetal, ketal or orthoester group G_9 ; wherein $G_9 = \text{Q}_1(\text{T}_1)(\text{T}_2)$; or

when $G_4 = \text{C}(\text{CHO}J_9)$ and $G_5 = \text{CH}(\text{O}J_{15})$, J_9 and J_{15} optionally are bonds from the oxygen atoms of G_4 and G_5 , respectively, to a carbon atom of an acetal, ketal or orthoester group G_{10} ; wherein $G_{10} = \text{Q}_1(\text{T}_1)(\text{T}_2)$; or